discharge, there was a significant difference found between the two groups for three muscle tests; chest press (p=.023), leg extension (p=.007) and the isometric right knee flexor test (p=.033). Though significant values were not reached on all tests, the differences between the pre- and post-scores of the two groups for all physical capacity tests are between 16% and 35%, suggesting that the intervention was efficient in preventing loss of and maintaining physical capacity.

Findings revealed that exercising patients during hospitalization for allo-HSCT was feasible, safe and effective. In conclusion, preventative and anticipatory interventions can minimize physical and functional loss during hospitalization for allo-HSCT.

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CO-STIMULATORY MOLECULE EXPRESSION BY TRANSPLANTED DONOR APC AND HOST CD4 T CELLS IS REQUIRED TO ELICIT RESISTANCE AGAINST MHC-MATCHED HEMATOPOIETIC ALLOGRAFTS FOLLOWING REDUCED INTENSITY CONDITIONING

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Circumventing host resistance to hematopoietic progenitor cell grafts is crucial for successful engraftment and the induction/maintenance of immune tolerance. We are studying the regulation of pathways that lead to T cell resistance in recipients transplanted with MHC-matched allogeneic BM ("MiHA-mis") following reduced intensity conditioning (RIC). To examine the involvement of CD80/CD86 expression in this resistance, CD80 and CD86 mabs were administered to B6 (wt) BMT recipients. Donor BALB.B BM was not rejected in these recipients. To investigate the requirement of CD80/86 expression on recipient cells with respect to development of resistance, BM was transplanted into wt or B6-CD80$^{-/-}$86$^{-/-}$ mice. Donor chimerism in both recipients was transient indicating resistance had been elicited against the donor BM. CD80$^{-/-}$86$^{-/-}$ BM was then transplanted into "MiHA-mis" recipients following RIC. In contrast to wt BM grafts, transplantation of CD80$^{-/-}$86$^{-/-}$ BM resulted in sustained donor chimerism. Since "MiHA-mis" BM transplants into CD4$^{-/-}$ recipients demonstrated CD4 cell function is critical for resistance in this model, we hypothesized that host CD4 cell recognition of donor APC results in the upregulation of CD80/CD86 co-stimulatory molecules. WT and CD40L$^{-/-}$ mice were transplanted with BALB.B BM and as predicted, wt recipients rejected the donor BM. In contrast, CD40L$^{-/-}$ recipients exhibited stable chimerism. To examine the requirement of CD40L on CD4 cells in the host, CD4$^{-/-}$ mice were transplanted with BM together with CD4 cells from wt or CD40L$^{-/-}$ mice. Recipients co-transplanted with wt CD4 cells rejected their grafts whereas recipients of CD4 cells from CD40L$^{-/-}$ donors expressed donor cell chimerism and failed to resist the MHC-matched BM allograft. We interpret the findings to demonstrate a requirement for host CD4 cells to recognize donor MiHA and undergo alloantigen induced activation resulting in CD40L induction of CD80/86 on donor APC. These interactions subsequently result in host CD8 cell effector activity inhibiting donor engraftment. Since recipients containing anti-donor specific CD8 memory cells were found to resist MHC-matched HCT containing CD80$^{-/-}$86$^{-/-}$ APC, these findings support the notion that direct recognition of donor APC is crucial to elicit T cell mediated resistance to hematopoietic engraftment in naive RIC MHC-matched allogeneic recipients. *Ex vivo* mab treatment of donor BM is being examined as a potential translational application.

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LOW RATES OF CHIMERISM OCCUR WHEN ALEMTUZUMAB IS ADDED TO CONDITIONING THERAPY FOR NON-MYELOABLATIVE ALLOGENEIC STEM CELL TRANSPLANTATION

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Non-myeloablative allogeneic stem cell transplantation (NST) aims to harness the graft-versus-tumor (GVT) effect while minimizing regimen-related toxicity, and relies on donor engraftment to induce remission. The most appropriate GVHD prophylaxis and preparative regimen in this setting remains poorly defined, though accumulating evidence suggests that full donor chimerism is associated with maximal GVT effects and protection from relapse. Previously we found a high rate of donor chimerism but a high incidence of severe GVHD using fludarabine (flu)/cyclophosphamide (Cy) conditioning and cyclosporine (CSA)/mycophenolate moftil (MMF) as GVHD prophylaxis. Subsequently, methotrexate (MTX) was substituted for MMF and alemtuzumab (100 mg over 5 days, days -9 to -5) has been added to our conditioning therapy in an attempt to both deplete host antigen-presenting cells as well as infused donor T cells and therefore minimize GVHD. Here we describe 55 patients who received NST; 23 were conditioned with chemotherapy alone and 33 were conditioned with alemtuzumab in addition to flu/Cy (n=31) or flu/melphalan (n=2). All received CSA/MTX post-transplant. The median age at NST was 50 years. Indications for transplant were Hodgkin's disease (13), NHL (22), MDS (7), CLL (5), myeloma (5) and 1 each with AML, breast cancer, and and ovarian cancer. Most patients were heavily pretreated and 62% had relapsed disease after prior autologous SCT. There were no significant differences between the groups that did and did not receive alemtuzumab. Donor chimerism was evaluated in all patients. 36% of patients conditioned with alemtuzumabhad sustainable chimerism over 90%, and 42% attained donor chimerism over 50%. This was significantly lower than in patients conditioned without alemtuzumab; 77% and 82% had sustainable donor chimerism >90% and >50% respectively (p<0.005). There was no significant difference in median survival between patients treated with (12 mo) and without (16 mo) alemtuzumab (p=0.36). Relapse rates appeared higher with alemtuzumab-containing regimens. Alemtuzumab at this dose and schedule markedly decreased the incidence of severe GVHD, but resulted in a higher incidence of graft-rejection and hence lower rates of full and mixed donor chimerism. Since full donor chimerism may be associated with freedom from relapse, alternative conditioning regimens, and alternative dosing and schedule of alemtuzumab administration (to deplete host APC without in-vivo T cell depletion of the donor graft) are being explored.

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OUTCOME OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR PEDIATRIC PATIENTS WITH CHRONIC MYELOID LEUKEMIA

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Although allogeneic hematopoietic stem cell transplantation (HSCT) from an HLA-matched sibling offers curative therapy for the small numbers of children who develop chronic myeloid leukemia (CML), less than one third of patients have an appropriately matched sibling. Alternative donor transplantation has had a higher procedure-associated risk, particularly for graft-versus-host disease (GVHD). We have attempted to reduce these risks by incorporating alemtuzumab (Campath 1H) into the preparative regimens for alternative donor grafts. Between 1996 and 2006, 19 pediatric CML patients were transplanted using either matched sibling (MSD; n = 9) or alternative donor (AD; 5 matched unrelated; 2 mismatched unrelated; 3 mismatched related). All recipients of MSD grafts were in chronic phase at the time of transplant as were 6 of the AD recipients; three of the AD recipients were in accelerated phase and 1 in chronic phase presenting in lymphoid blast crisis at the time of transplant. All recipients received myeloablative conditioning consisting of cyclophosphamide 45mg/kg x 2, cytarabine arabi-